Standardized Reporting of Microscopic Renal Tumor Margins: Renal Tumor Capsule Invasion (*i*-Cap) Scoring System

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KEY OF DEFINITIONS FOR ABBREVIATIONS:

i-Cap: Capsule Invasion Scoring System
IUH: Indiana University Hospital
LUMC: Loyola University Medical Center
RN: Radical Nephrectomy
HM: Healthy Margin Partial Nephrectomy
EN: Enucleation Partial Nephrectomy
RCC: Renal Cell Carcinoma
BMI: Body Mass Index
SIB: Surface-Intermediate-Base
IQR: Interquartile Range

Abstract

Purpose:

Renal tumor enucleation allows for maximal parenchymal preservation. Identifying pseudocapsule integrity is critically important in nephron sparing surgery by enucleation. Tumor invasion into and through capsule may have clinical implications although it is not routinely commented on in standard pathologic reporting. We sought to describe a system to standardize the varying degrees of pseudocapsule invasion and to identify predictors of invasion.

Materials and Methods:

A multicenter retrospective review was carried out between 2002-2014 at Indiana University Hospital (IUH) and Loyola University Medical Center (LUMC). 327 tumors were evaluated following removal via radical (RN), healthy margin partial (HM), or enucleation (EN) partial nephrectomy. Pathologists scored tumors using our invasion of pseudocapsule (*i*-Cap) scoring system. Multivariate analysis was performed to determine predictors of higher score tumors.

Results:

Tumor characteristics between surgical resection groups were similar. Enucleated tumors tended to have thinner pseudocapsule rims but did not demonstrate higher *i*-Cap scores. Rates of complete capsular invasion (*i*-Cap 3) were similar between surgical techniques and comprised 22% of the overall cohort. Papillary histology along with increasing tumor grade was predictive of an *i*-Cap 3 score.

Conclusions:

A capsule invasion scoring system is useful in classifying renal cell carcinoma (RCC) pseudocapsule integrity. *i*-Cap scores appear independent of surgical technique. Complete capsular invasion is most common in papillary and high-grade tumors. Further work regarding the relevance of capsular invasion depth as it relates to oncological outcome in both local recurrence and disease specific survival is warranted.

INTRODUCTION:

Partial nephrectomy (PN) remains the preferred surgical therapy for renal masses less than 7 centimeters whenever feasible secondary to the well described benefits of nephron preservation and equivalent oncologic outcomes when compared to radical nephrectomy.[1,2] Tumor enucleation (TE) is a nephron sparing surgical technique, commonly employed in patients with hereditary renal syndromes, which maximally preserves normal renal parenchyma.[3] Recently, a tumor enucleation approach has become more prevalent in the surgical management of sporadic renal masses with promising initial results.[4,5]

Renal tumor enucleation takes advantage of the renal tumor pseudocapsule, consisting of a fibrous band of compressed renal parenchyma that isolates the tumor from the surrounding healthy renal parenchyma and provides a natural dissection plane during surgery (Figure 1).[6] When compared to healthy margin partial nephrectomy for RCC, tumor enucleation has demonstrated comparable oncological outcomes in some series.[7] Opponents of this technique caution that the integrity of the tumor pseudocapsule may predict the presence of a positive surgical margin. Although several publications have suggested that the presence of a positive margin does not predict tumor recurrence after partial nephrectomy, pathologic invasion of the tumor pseudocapsule may play an important role in predicting cancer recurrence and overall worse outcomes.[8-12] Surgeons have recently purposely enucleated renal tumors at the base of the tumor/parenchymal interface, leading to a new standardization of surgical technique reporting.[5]

Currently, there are no protocols for pathologists to use to characterize the integrity of the renal tumor pseudocapsule and the status of the pseudocapsule (presence, absence, invasion into) is not standardly reported to the treating urologist. In collaboration with the pathology and urology departments at our respective institutions, we sought to create a simple and easily reproducible scoring system (*i*-Cap) to assess the integrity of the renal tumor pseudocapsule and used this system to evaluate pathologic specimens treated over a 12-year period. In addition, we investigated the clinical parameters that may ultimately serve as pseudocapsule integrity predictors that may influence pre-surgical evaluation in an attempt to improve future patient outcomes.

MATERIALS AND METHODS:

Patient Selection:

A multicenter retrospective cohort study was carried out at Indiana University Hospital (IUH) and Loyola University Medical Center (LUMC) from October 2002 – December 2014. Patients who underwent renal surgery with clear, papillary or chromophobe histologic subtypes were included in the study. Patients with clinical T1 staging preoperatively were included in this study, while higher staged, more aggressive tumors were excluded from this study. Patients with benign renal tumors such as oncocytoma and angiomyolipomas were excluded. Overall, 327 patients who underwent radical (RN), healthy margin partial (HM) or enucleation (EN) partial nephrectomy were included.

Pathologic Assessment:

Trained genitourinary pathologists at each institution reviewed each pathological specimen. Tumors were staged according to the pTNM guidelines in the 7th edition of the American Joint Committee on Cancer (AJCC) Staging Manual and graded according to the criteria set out by the Fuhrman grade system.[13,14] Tumor characteristics such as histologic subtype, mean pseudocapsule thickness, pseudocapsule completeness, presence and extent of pseudocapsular invasion, and surgical margin status were reviewed. Sections from the entire tumor-parenchymal interface were examined in all cases.

Each tumor also received an *i*-Cap score between 1-3 in accordance with the designed pseudocapsular invasion (*i*-Cap) scoring system (Figure 2). *i*-Cap scores of 1 were assigned to tumors with completely intact pseudocapsule without cancerous invasion. *i*-Cap scores of 2 were assigned to tumors that either had focal absences within their pseudocapsule without invasion or cancerous tissue invasion partially into, yet not completely through the pseudocapsule. *i*-Cap scores of 3 were assigned to tumors that had completely lost pseudocapsule integrity where carcinoma extended into surrounding healthy parenchyma (Figure 2).

Statistical Analysis:

Clinical and demographic variables were compared across sites and by surgical techniques. Chi-square tests, and fisher's exact tests when appropriate, were used for categorical comparisons; while independent t-tests and one-way ANOVAs were used for continuous comparisons. Multivariable binary logistic regression was then performed to assess predictors of *i*-Cap 3 tumors, versus *i*-Cap 1 and 2 tumors, via a stepwise selection procedure and AIC criterion. Statistical significance was assessed at an $\alpha=0.05$ level and all analyses were conducted using SAS v9.4 (SAS Institute, Cary NC).

RESULTS:

A total of 327 patients participated in this study over the years of 2002-2014. Two hundred and four of these patients received care at Loyola University Medical Center while 123 patients received care at Indiana University Hospital. Baseline patient demographics and tumor characteristics are shown in Table 1. The median age was 55 years old (IQR 46-65). The majority of patients were male (213, 65.1%) and Caucasian (262, 80.1%) with a median BMI of 29.8 kg/m^2 (IQR 26-35.4).

Radical, healthy margin, and enucleation partial nephrectomy were performed in 132, 151, and 44 patients, respectively. The mean tumor size was 3.03 cm (SD 1.3 cm). Clear cell renal cell carcinoma was the most prevalent histology (208, 63.6%) while 90 (27.5%) tumors were papillary and 29 (8.9%) were chromophobe. The majority of patients had pT1a (267, 81.7%) and Fuhrman grade 2 (207, 64.7%) tumors on final pathology. Tumor characteristics varied between institutions in terms of both histology and stage ($p<0.001$). Tumors removed at Indiana University were more widely distributed in terms of histology while tumors removed at Loyola University were more commonly clear cell (148, 72.5% vs. 60, 48.8%). Those tumors removed at Indiana University were also more commonly staged pT1b when compared to that of the Loyola University population (33 (26.8%) vs. 21 (10.3%)).

Invasion into the pseudocapsule (*i*-Cap) scores were assigned to all tumors included for analysis. *i*-Cap 1, 2 and 3 were assigned to 79 (24.2%), 176 (53.8%) and 72 (22%) tumors, respectively. *i*-Cap scores were distributed evenly amongst surgical technique ($p=0.09$) except for *i*-Cap 3 tumors which were less prevalent with tumor enucleation (16%) when compared to RN (25%) and HM (21%). Mean pseudocapsule thickness was 0.77 cm (SD 0.69). Pseudocapsule thickness was dependent on surgical technique as thinner pseudocapsules were observed in the enucleation group with mean pseudocapsule thickness in the radical nephrectomy group was 0.77, healthy margin 0.83, and enucleation partial nephrectomy 0.54 cm ($p=0.047$). Positive surgical margins were present overall in 11 (3.4%) cases. Ten of the 11 patients who had a positive surgical margin underwent healthy margin partial nephrectomy, while the remaining positive margin underwent radical nephrectomy. None of the patients who underwent tumor enucleation had a positive margin on pathologic analysis.

Multivariate analysis was completed to investigate factors associated with renal tumors more likely to demonstrate a higher *i*-Cap score (complete invasion). Results are demonstrated in Table 3. Of note both surgical technique (radical nephrectomy vs healthy margin partial nephrectomy vs enucleation partial nephrectomy) and pseudocapsule thickness were not predictive of tumors having an *i*-Cap score of three. Tumor histology appeared to impact higher

i-Cap 3 scores with papillary type renal cell carcinomas carrying the highest risk (OR 3.04, CI 1.52-6.09, p=0.002). Increased risk of *i*-Cap 3 score was also seen in tumors with higher Fuhrman grade with grade 4 carrying the highest risk (OR 14.68, CI 2.16-123.18, p=0.007). *i*-Cap 3 tumors were also more prevalent in the Loyola University population compared with the IU group (OR 2.26, CI 1.04-4.88, p=0.04). Patients with a higher BMI demonstrated modest increases in *i*-Cap scores when compared to smaller counterparts (OR 1.05, CI 1.01-1.10, p=0.01).

DISCUSSION:

Nephron sparing surgery where technically feasible is the standard of care for clinical T1 renal masses.[1] The literature has demonstrated the amount of parenchyma spared during these resections can directly correlate to improved long-term functional outcomes.[15,16] In light of these observations, parenchymal function preservation has been pursued through means of focusing on either reduction in warm ischemic time or maximization of spared renal parenchyma tissue during extraction. Enucleation partial nephrectomy provides the opportunity to achieve both of these ends while producing oncological outcomes comparable to those achieved with healthy margin partial nephrectomy.[7,17-20] Enucleation leverages the integrity of the pseudocapsule surrounding it in order to maintain negative surgical margin status.[6,10-12] Our study was able characterize and classify the tumor pseudocapsule in T1 RCC by evaluating degrees of integrity and invasion in a previously operated set of patients. Additionally, we were able to determine that tumor grade and tumor histology may play a significant role in predicting a higher invasion (*i*-Cap) score. We hope that that this simple scoring system may be adopted, studied, and implemented by the evaluating pathologist when reporting to the managing urologist.

Initially developed as an intervention for hereditary renal syndrome patients, tumor enucleation utilizes the pseudocapsular-parenchymal interface via blunt dissection along natural cleavage planes while sparing healthy surrounding parenchyma.[3,21] The close border between tumor and healthy renal tissue manipulated during the enucleation creates concern regarding margin status and the potential for iatrogenic rupturing of the pseudocapsule during extraction, which may impact pathologic processing.[22] Despite this, multiple studies done by Minervini et al. have demonstrated that even a relatively thin pseudocapsule successfully guards against iatrogenic increases in positive margin rates.[11,12] Our data displayed positive surgical margin rates of 3.4% for all cases, with none occurring in the enucleation group. Despite the absence of increased margin rates, we observed the thinnest pseudocapsule in the enucleation group compared with other groups, suggesting that some degree of pseudocapsule may be altered when utilizing this technique. If tumor pseudocapsule invasion was principally a function of pseudocapsule thickness it may be assumed that the enucleation group would have the highest *i*-Cap scores. The opposite was true when analyzing our data with the lowest *i* Cap 3 rates found in the enucleation cohort. Whether this was a function of the technique or a byproduct of appropriate selection remains unknown. In any event it at least suggests that surgical technique –healthy margin versus enucleation partial nephrectomy— is not a critical predictor of capsule invasion and in it of itself should not dissuade surgeons from considering tumor enucleation as a viable option.

The tumor pseudocapsule has been well described as a fibrous band of compressed renal parenchymal tissue encompassing most renal cell carcinoma. The integrity of the pseudocapsule

may vary greatly depending on the histological features of the tumor it surrounds.[11,23,24] Previous literature has demonstrated that tumor subtype may be predictive of pseudocapsule characteristics.[11,12,24] Additionally, higher rates penetrating pseudocapsule disease in RCC may be seen in patients with of higher Fuhrman grade tumors and more advanced TNM stage.[6,8-10,23] In the current study, *i*-Cap scores of 1, 2 and 3 were assigned to 79 (24%), 176 (54%) and 72 (22%) tumors, respectively amongst the entire cohort. Tumors scored as *i*-Cap 2 made up largest percentage of the cohort. *i*-Cap 3 scored tumors demonstrate complete loss of pseudocapsule integrity with penetration of tumor directly into surrounding parenchyma and carry the highest risk for loss of negative margin status. Although currently debated, early studies of the clinical implications of positive margins demonstrated a higher risk of tumor recurrence and should be avoided in all cases.[25,26] Even when a positive margin never evolves into a clinically significant recurrence, the impact of rigorous surveillance may carry with it both a financial and emotion burden to the patient[27,28] The i-Cap scoring system can provide an essential tool not only to the pathologist but also to the treating urologist to aid in the creation of an appropriate post-operative care plan for the renal cell cancer patient.

Considering the importance of positive margins status and concurrent loss of pseudocapsule integrity, multivariate analysis was carried out during this study to investigate factors associated with i-Cap 3 tumors that may be preoperatively assessable through means of biopsy and imaging. In our analysis papillary type renal cell carcinomas carry the highest chances of i-Cap 3 scores compared to that of other histologic subtypes (OR 3.04, CI 1.52-6.09, p=0.002). Increasing risk of i-Cap 3 score was also observed in higher Fuhrman grade tumors with grade 4 carrying the highest risk (OR 14.68, CI 2.16-123.18, p=0.007). We believe this data implies that papillary histology and highly aggressive nuclear features observed on biopsy require special attention to margin status during the perioperative period. This study may also suggest that regardless of small tumor size, enucleation may not be clinically indicated in tumors exhibiting these histologic features.

Creating a pseudocapsule scoring system that is easily implemented and interpreted is becoming increasingly important as interest in the consideration of enucleation partial nephrectomy in the sporadic solitary renal mass is expanding. Indeed, there is an effort to codify surgical approaches where enucleation is variably or partially employed in the surgical approach. A recent study conducted by Kutikov et al., the surface-intermediate-base (SIB) margin score was created as a means of commenting on the macroscopic remnant pseudocapsule surrounding the tumor.[5] The authors attempted to validate the scoring system in a follow up analysis.[29] The SIB scoring system provides is predicated on the surgeon's ability to accurately assess the presence or absence of residual parenchyma around various sections of the removed renal tumor. The *i*-Cap

scoring system, determined by histopathological analysis, may function as an ideal complement to aforementioned SIB system in that it may provide a checks and balances to the surgeon's assessment on a microscopic level. This could allow for improvement in the standardization of reporting and hopefully provide a valuable tool for tumor prognostication. Clearly, the ultimate utility and integration of both scoring systems for renal cell carcinoma have yet to be fully defined.

The current study carries notable limitations. Pathologic scoring was done in a retrospective fashion after the initial pathologic review was already completed. Additionally, some *i*-Cap scores may have been upgraded secondary to iatrogenic disruption of the pseudocapsule during surgical removal and/or specimen processing. Inter-observer variation and institutional biases may have existed amongst pathologist grading the pseudocapsule integrity. Although the *i*-Cap scoring system is a quality tool to standardize the assessment of the renal tumor pseudocapsule, the clinical implication of this grading tool has yet to be defined and will require longer follow up. These limitations notwithstanding, this represents the first described attempt to classify the integrity of the tumor pseudocapsule through the creation of easy and simple reproducible scoring system for renal cell carcinoma.

CONCLUSION:

Our study proposes a capsule invasion scoring system that may be useful in further classifying the tumor pseudocapsule integrity in small renal masses. Although tumor enucleation may attenuate the pseudocapsule, integrity of the capsule appears to be independent of surgical technique. Complete tumor pseudocapsule invasion into surrounding renal parenchyma appears most common in papillary histologic subtype and high-grade tumors. Further work regarding the implementation of the *i*-Cap scoring system and investigating the clinical implication of higher *i*-Cap scores is warranted.

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TABLES:

Table 1. Patient Population by Institution

Variables (%/Standard Deviation)	Loyola University Medical Center N=204	Indiana University Hospital N=123	Total N=327	p-value
Sex				0.49
Male	130 (63.7%)	83 (67.5%)	213 (65.1%)	
Female	74 (36.3%)	40 (32.5%)	114 (34.9%)	
Race				<0.001[a]
White	154 (75.5%)	108 (87.8%)	262 (80.1%)	
African American	22 (10.8%)	13 (10.6%)	35 (10.7%)	
Hispanic	22 (10.8%)	0 (0%)	22 (6.7%)	
Asian	6 (2.9%)	2 (1.6%)	8 (2.4%)	
Median Age (IQR)	54 (46-65)	57 (47.5-68.5)	55 (46-65)	0.10
Median BMI (IQR)	30.8 (26.4-36.1)	28.2 (25.6-33.4)	29.8 (26.0-35.4)	0.01
Surgical Technique				<0.001
Healthy Margin	82 (40%)	69 (56%)	151 (46.2%)	
Radical	78 (38%)	54 (44%)	132 (40.4%)	
Enucleation	44 (22%)	0	44 (13.4%)	
Histologic Subtype				<0.001
Clear Cell	148 (72.5%)	60 (48.8%)	208 (63.6%)	
Papillary	43 (21.1%)	47 (38.2%)	90 (27.5%)	
Chromophobe	13 (6.4%)	16 (13.0%)	29 (8.9%)	
Pathologic Stage				<0.001[a]
T1a	177 (86.8%)	90 (73.2%)	267 (81.7%)	
T1b	21 (10.3%)	33 (26.8%)	54 (16.5%)	
T3a	6 (2.9%)	0 (0%)	6 (1.8%)	
Fuhrman Grade‡				0.08
1	17 (8.6%)	4 (3.3%)	21 (6.6%)	
2	124 (62.9%)	83 (67.5%)	207 (64.7%)	
3	48 (24.4%)	35 (28.5%)	83 (25.9%)	
4	8 (4.1%)	1 (0.8%)	9 (2.8%)	
***i*-Cap Score**				0.02
1	42 (20.6%)	37 (30.1%)	79 (24.2%)	
2	108 (52.9%)	68 (55.3%)	176 (53.8%)	
3	54 (26.5%)	18 (14.6%)	72 (22.0%)	
Size (cm)	2.85 (1.17)	3.31 (1.54)	3.02 (1.3)	0.004
Mean Pseudocapsule Thickness (cm)	0.50 (0.44)	1.21 (0.80)	0.77 (0.69)	<0.001
Positive Surgical Margin	2 (1%)	9 (7.3%)	11 (3.4%)	0.003[a]

Note: Chi-square test used for all categorical variables unless otherwise noted. Independent t-tests used for continuous variables. a. Fisher's exact test used due to small expected cell counts
‡ N=7 (3.4%) of LUMC tumors did not have a Fuhrman grade

Table 2. Cohorts Examined by Surgical Technique

Variables (%/Standard Deviation)	Healthy Margin N=151	Radical N=132	Enucleation N=44	p-value
Histologic Subtype				0.57
Clear Cell	100 (66%)	80 (61%)	28 (64%)	
Papillary	36 (24%)	40 (30%)	14 (32%)	
Chromophobe	15 (10%)	12 (9%)	2 (5%)	
Pathologic Stage				0.27[a]
T1a	120 (79%)	111 (84%)	36 (82%)	
T1b	26 (17%)	21 (16%)	7 (16%)	
T3a	5 (3%)	0 (0%)	1 (2%)	
Fuhrman Grade				0.047[a]
N/A	1 (0.5%)	5 (3.8%)	1 (2.5%)	
1	10 (7%)	5 (3.8%)	6 (14%)	
2	97 (64%)	79 (60%)	31 (70%)	
3	41 (27%)	37 (28%)	5 (11%)	
4	2 (1.5%)	6 (4.4%)	1 (2.5%)	
***i*-Cap Score**				0.09
1	28 (19%)	39 (30%)	12 (27%)	
2	91 (60%)	60 (45%)	25 (57%)	
3	32 (21%)	33 (25%)	7 (16%)	
Mean Size (cm)	2.94 (1.4)	3.12 (1.4)	3.02 (1.09)	0.53
Mean Pseudocapsule Thickness (cm)	0.83 (0.75)	0.77 (0.68)	0.54 (0.41)	0.047
Positive Surgical Margin	10 (6.6%)	1 (0.8%)	0 (0%)	0.01[a]

Note: Chi-square test used for all categorical variables unless otherwise noted. Independent t-tests used for continuous variables. a. Fisher's exact test used due to small expected cell counts

Table 3. Clinical Predictors of Pseudocapsule Invasion (*i*-Cap 3) Analysis

Multivariable Analysis	Odds Ratio	(95% CI)	p-value
BMI	1.05	(1.01-1.10)	0.01
Site			0.04
IUH	REF		
LUMC	2.26	(1.04-4.88)	0.04
Histologic Subtype			0.01
Clear Cell	REF		
Papillary	3.04	(1.52-6.09)	0.002
Chromophobe	0.52	(0.12-2.23)	0.38
Pathologic Stage			0.02
T1a	REF		
T1b	0.45	(0.16-1.27)	0.14
T3a	14.68	(1.51-143.09)	0.02
Fuhrman Grade			0.008
1	REF		
2	1.50	(0.39-5.76)	0.55
3	3.01	(0.73-12.38)	0.13
4	16.33	(2.16-123.18)	0.007

FIGURES:

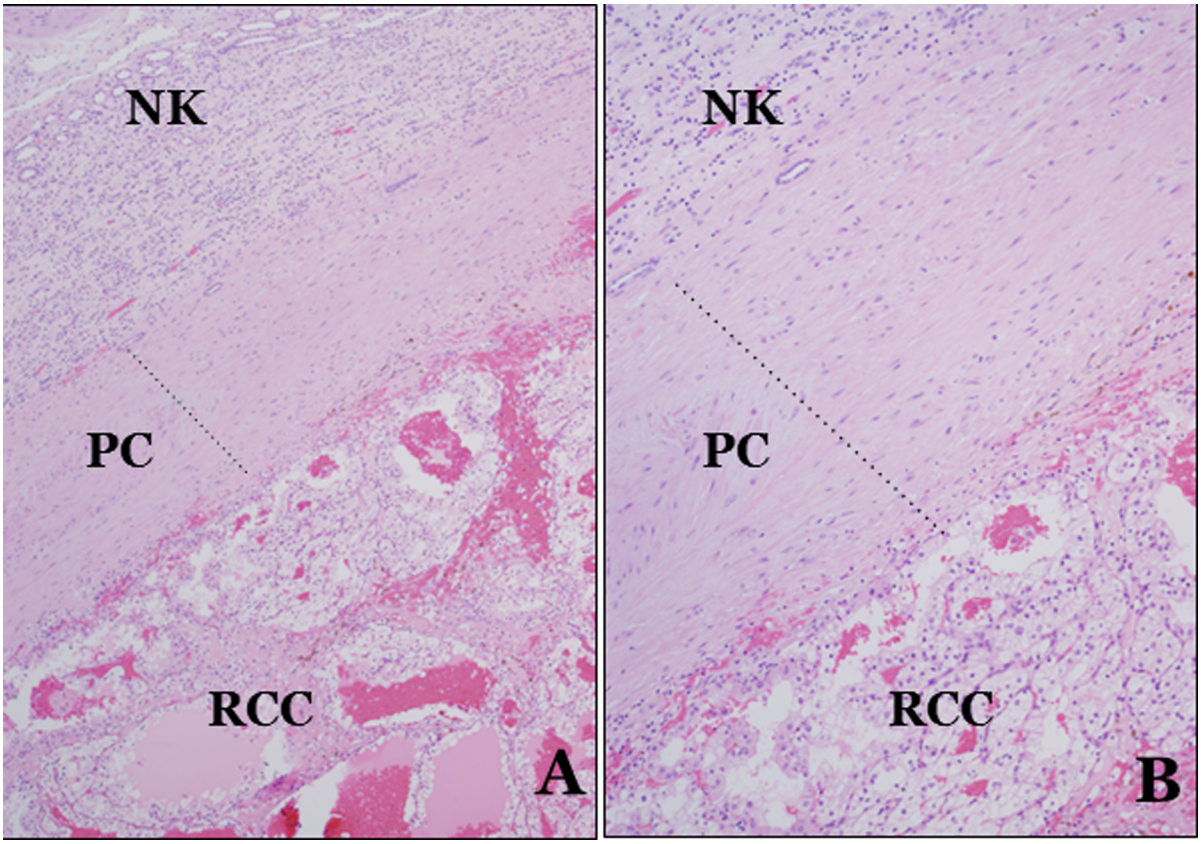


Figure 1. Microscopic Investigation: A) 5x Magnification B) 10x Magnification.
Clear Cell Renal Cell Carcinoma with Intact Pseudocapsule: Inferior portion of figure exemplifies carcinoma isolated from superior portion of healthy parenchyma by pseudocapsule. KEY: Normal Kidney (NK), Pseudocapsule (PC), Renal Cell Carcinoma (RCC)

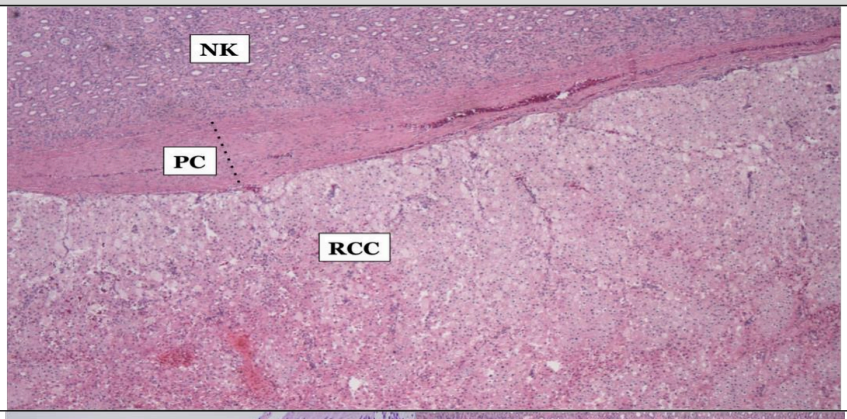
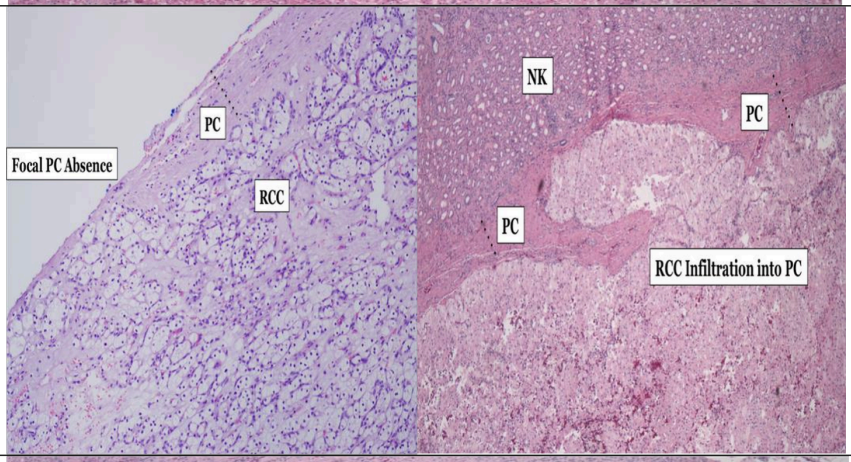
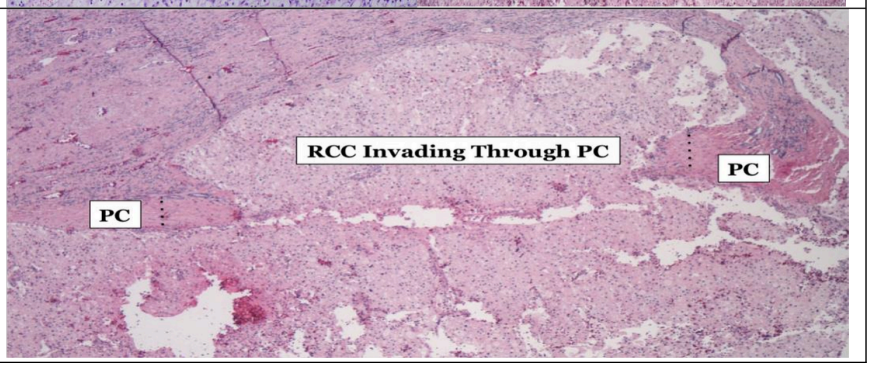
i-Cap Score	Description	Representative Image
1	Pseudocapsule is completely intact on the normal parenchyma side.	
2	Pseudocapsule has either a focal absence or <100% infiltration of carcinoma into the PC but not into the normal parenchyma.	
3	Any degree of carcinoma infiltration completely through the PC and into the normal parenchyma.	

Figure 2. i-Cap Scoring System. All pictures taken under 10x magnification.
KEY: Normal Kidney (NK), Pseudocapsule (PC), Renal Cell Carcinoma (RCC)